

The Need for Laws and Regulations on Biotherapeutics

Executive Summary

The advancing industry of biotherapeutics is providing the public with new promising, innovative drugs which may pose risks if their production, distribution, and marketing are not directly governed by legislation. Apart from international agreements, such as the Cartagena Protocol, there are no specific and direct laws or regulations governing manipulated cell-based therapeutics in Canada. The introduction of these laws and regulations in Canada will allow for the safe research and use of biotherapeutics in a proactive manner.

Background

The emerging biotechnology sector in the global economy and the vast amount of research into engineered cell-based therapeutics alludes to the imminent creation and marketization of engineered cell-therapy drugs (hereby referred to as biotherapeutics). Effective planning of regulations and economics will be necessary to better prepare for the introduction of these biotherapeutics into the market. Specific regulations can both serve to encourage expansion in this novel field, deter misuse of this technology, and to prevent potential incidents that elicit risks from the use of this group of drugs. Biotherapeutics has been appraised to become the “third pillar” of pharmaceuticals after synthetic chemicals and biologics in the research community. Much of the laboratory research on biotherapeutics is expected to go through clinical trial phases in early 2018 . North America has experienced tremendous growth in the biotechnology sector in the last 5 years, with the number of biotechnology companies increasing by 400% since 2011. The biotechnology sector currently totals 111.2 billion dollars of annual revenue. Furthermore, 68.4% of the biotechnology companies have main focuses on human health technologies, which is evidence for the increasing availability and prevalence of biotherapeutics. An appropriate policy framework would thus need to be installed to ensure these technologies are properly regulated and contained. Policy frameworks will also serve to streamline the process of bringing biotherapeutics to the market. The current Health Canada regulatory frameworks (and international standards) are shaped to address potential incidences with chemically synthesized drugs, some biologics products, and some stem cell therapy applications. These Health Canada regulations give some mention to synthetic biology/genetically engineered products, but these are descriptive at best. Prior experiences pertaining to the introduction of biologics has elucidated the importance of parallel development of technological discoveries and policy to avoid early accidents. Early planning for preventative purposes is particularly important for biotherapeutics due to the rapid and far-reaching consequences that could occur if misused.

Fragmentation of applicable regulatory policies in separate guidance documents, the dispersion of responsibilities across ministries and agencies, and limited infrastructure appropriate for manufacture of this novel technology could pose potential challenges in implementation. Biotherapeutics would be governed under many separate guidance documents under the current framework, particularly a combination of cell-based therapeutics and gene therapy documents. This separation leaves many regulatory gaps where the interactions between separate genes, between genes and cell types are not considered. Not having specific guidelines also deters individuals from going into this field, which impedes its growth.

This policy brief presents strategies that can build an effective policy framework for biotherapeutics and develop a comprehensive knowledge base on biotherapeutics in order to guide, accelerate and improve action.

Strategies for action

The introduction of specific regulations pertaining to the development, manufacturing, and ongoing surveillance of biotherapeutics is pertinent to facilitate the safe and effective use of this drug technology. For such regulations to be practical:

- They should build off of existing framework
- They must involve the coordinated efforts of relevant ministries, academic institutions, companies, and other relevant partners
- They need the financial and technical support of governmental institutions
- They need the political confirmation and support of international institutions

The strategies outlined below should be seen as complementary to one another but must be implemented concurrently for maximum impact

Adaptive Drug Assessment Process

The United States Environmental Protection Agency has classified intergeneric microorganisms as being distinct from other microorganisms and has created regulations specific for them. Canada should adopt a similar policy regarding modified microorganisms that account for their unique properties, namely the likelihood of emergent properties. Emergent properties refer to the possibility of unpredictable phenotypes arising due to the interactions of introduced genes with native genes, other cellular components, or other cells. Because of the unpredictability of emergent properties, it will be necessary to improve current risk assessment procedures as well as introduce long term plans for effective monitoring of manipulated cells once they are released onto market.

Currently, regulations for microorganisms released into the environment, whether as products intended for use by humans or not, do not have any provisions for long term monitoring in case of changes to the properties and characteristics of the organism or any products it produces. As well, limited risk assessment tools make it difficult to properly predict, control for, and reduce the risks associated with emergent properties.

Standard Indicators

Although there is no single standard that can reveal the entire complexity of whether a biotherapeutic will have undesired side effects, a number of design specifications of a biotherapeutic technology should be considered when assessing the safety of the technology. These design specifications include, but are not limited to:

- Presence of Kill-switch technology (genes incorporated such that certain environmental exposure causes the cell to commit to apoptosis)
- Presence of Auxotrophy (knocking out genes for essential nutrients for the cell so that it will not be able to survive without an abundance of said nutrient in its immediate surroundings)
- Report on reproductive capabilities of cell product
- If the cell type is likely to retain integrated genes for an extended period of time (linked to the insertion site of gene, ex. Plasmid vs. chromosome)
- Promoter strength (how likely gene is to be transcribed and translated into product) is closely tied to dosage

- Cell type and origin
- Gene type and origin
- Differentiate *in vivo* vs. *ex vivo* transformations

Users should be aware that any one of these points would not be necessary to assess the safety of a particular product, reference to multiple standardized indicators may be necessary. Benefit-risk analysis should be conducted with reference to standardized indicators on a case-by-case basis. Standardized indicators could offer a fast way to review incoming biotherapeutic proposals, although it will need to work in conjunction with current assessments to inform decision regarding drug approvals.

Improved pharmacovigilance practices

In order to best implement biotherapeutics technologies for use in the future, it is important for pharmacovigilance practices to be up to the same standards as the drug approval process. This is especially important for biotherapeutics due to proliferative and adaptive properties of cells making even the smallest contamination issue potentially far-reaching and detrimental. Numerous systematic reviews have cited the pitfalls of Canada's current pharmacovigilance system particularly the issues of under-reporting of adverse drug events and long processing times. Qualitative study of Canadian pharmacovigilance conducted by Nichols et al. identified that only 3% of all adverse reactions actually get reported, and overall reviewing times take months after the actual occurrence of the adverse drug event. Under these circumstances, even modest modifications could yield significant results. There are a few modifications to consider:

- Increase reporting frequency by encouraging participation of both community and institutional pharmacists, physicians, and affiliated institutions; and Open up the option of individual patient reporting of adverse drug events
- Impose accountability measures for companies and professionals that do not report adverse events in compliance with good pharmacovigilance practices, and for mishandling or intentional release of products
- Intuitive online reporting system with categorical data that is easily compiled for reviewing purposes
- Coordinated effort between epidemiologic personnel in the Public Health Agency of Canada and pharmacovigilance review board to react quickly to adverse events or leaks

Optimal use should be made of the above strategies, but there are certain limitations to each and alternative strategies might be necessary. These modifications are meant to be restricted to any future biotherapeutic products as implementation for all drugs could be costly and cumbersome.

Build Local Expertise and Know-how

Historically, the release of any novel technology has faced opposition from the public and lobby groups due to lack of understanding. Often, individuals who might benefit from the technology miss the opportunity due to misconceptions and stigmas. For these reasons, training and public education are particularly vital to avoid misuse and to obtain maximum benefit. Training with these new technologies should be extended to relevant ministries, authorized health professionals, and community advocates. In terms of content, the training should involve both theoretical science and hands-on handling skills of each biotherapeutic. Individuals should know basic operation as well as basic troubleshooting and emergency reaction protocols by the end of training. Public education about the science behind genetically engineered devices is also vital to

prevent stigmatism. This involves an integrated effort between education boards and health ministries. The advantages of professional training and public education include the access of biotherapeutics by individuals who need them to maximize societal benefit, as well as minimizing incidence of misuse.

International harmonization

Biotherapeutics also offer many advantages in foreign settings, such as ease of use, minimal maintenance, and self-reproducibility. With increasing international travel and migration, there is increasing demand for the pharmaceutical industry to be regulated on the global scale, not to mention that development in the biotechnology industry is occurring all around the globe. Local, national, and international efforts are needed to gain more insight on the potential ways to increase safety and efficacy of biotherapeutics; this may include specific international guidelines established through the International Conference of Harmonization (ICH).

Build Innovative Research Networks

Ensuring the safety and efficacy of biotherapeutics should involve coordinated efforts across many sectors – health, education, labor, civil service and the private sector – and the Canadian regulatory system, academic institutions and other stakeholders. It is therefore important to set up and strengthen mechanisms that bring together producers, regulators, and end users of biotherapeutic products. This could be achieved by increasing awareness and funding about biotherapeutics in government.

Potential benefits include increasing drug research innovativeness, consolidation between the lab bench and the public, and higher ability to better address health demands while still being strict on issues like bioterrorism. The Cartagena Protocol is a step that the international community has taken to get closer to increasing cooperation between sectors, and makes good points regarding the development of biotherapeutics. In practice, such a network does not exist as of yet on the international scale. Canada, as an international leader of progressive health policies, should develop strategies toward this end.

Conclusion

The advancing industry of biotherapeutics is supplying society with novel promising drugs which may pose risks if their production, distribution, and marketing are not governed by legislation. As there are no specific regulations in Canada governing manipulated cell-based therapeutics, the introduction of these laws and regulations in Canada will be beneficial in authorising the safe research and use of biotherapeutics. Strategies attempting to address this gap in therapeutic regulation should include an adaptive drug licensing process which makes use of existing standard indicators commonly used by researchers, a cooperative pharmacovigilance strategy for post-market monitoring, as well as a local and international research network which increases access to biotherapeutics for those who need it while preventing misuse and bioterrorism acts.